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*The application was originally filed in English.*

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*Lisa Junegren*

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# MANUFACTURING PROCESS FOR NO-DONATING COMPOUNDS

## FIELD OF THE INVENTION

The present invention relates to a new process for the preparation of NO-donating compounds using a sulfonated intermediate. The invention relates to new intermediates prepared therein suitable for large scale manufacturing of NO-donating compounds. The invention further relates to the use of the new intermediates for the manufacturing of pharmaceutically active NO-donating compounds.

## BACKGROUND TO THE INVENTION

NO donating compounds are compounds having a NO or $NO_2$ group linked to the pharmaceutically active compound. A linker may be used between the pharmaceutically active compound and the NO or $NO_2$ group.
The advantage of NO donating compounds compared to the parent compound are among others a good tolerance and the reduction of gastrointestinal side effects. This is especially true for NO donating analogues of NSAIDs such as diclofenac and ketoprofen.
NO donating analogues of NSAIDs are known for their pharmaceutical activity as antiinflammation and/or analgesic agents.

Different processes for the preparation of NO donating compounds have been described in the prior art.

In Cainelli, et al. (Tetrahedron Lett., 1985, 28, 3369-3372) and Cainelli, et al. (Tetrahedron 1985, 41, 1385-1392), the substitution of sulfonate esters with tetrabutylammonium nitrate or an ion-exchanger with nitrate ions in a solvent such as pentane, toluene or benzene, is described. During this process high temperatures are used, which makes the process unsafe to use for large scale production.

Cainelli, et al. (J. Chem. Soc. Perkin Trans. I, 1987, 2637-2642) describe the nitrate substitution of sulfonate esters by reacting alkylmethanesulfonates with tetrabutylammonium nitrate in toluene.

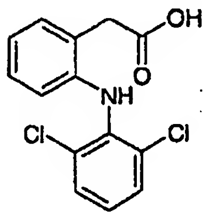
In Kawamura, et al. (Chem. Parm. Bull., 1990, 38, 2092-2096) an alkylphenylsulfonate is reacted with tetrabutylammonium nitrate in toluene.

The costs for the tetraalkylammonium nitrate sources used in stoichiometric amounts as described in these prior art documents are economically undesirable for large-scale manufacturing of NO donating compounds. Processes wherein cheaper and low molecular weight alkali metal nitrates may be used are preferred for economical reasons. However, tetraalkylammonium nitrates may be used as phase transfer catalysts in substoichiometric amounts.

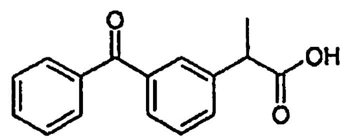
In Hwu, et al. (Synthesis, 1994, 471-474) the preparation of nitrate esters from sulfonic acid esters is described. The rather high temperatures and long reaction times used in combination with the low stability of the end products obtained, makes this process less suitable for large-scale production. In addition, the molar excess of sodium nitrate is at least twice as large as in the present invention, which increases costs and may give more waste problems. Further, the crude product obtained by the method according to Hwu et al, needs to be purified either by way of chromatography or distillation to obtain a pharmaceutically acceptable purity. Neither of these two purification options are appreciated for the large scale manufacturing of NO donating compounds.

ES 2,073,995, discloses the syntheses of alkyl nitrate esters from alkylsulfonates or 4-toluenesulfonates and metal nitrates using solvents such as dimethyl formamide, dimethyl acetamide, acetonitrile or dimethylsulfoxide. Using dimethyl acetamide or dimethylsulfoxide as solvent in the synthesis of NO donating compounds starting from for instance sulfonated intermediates gives a crude product which needs to be purified either by chromatography or by distillation to achieve a pharmaceutically acceptable quality.

Examples of NSAIDs are diclofenac (compound of formula Ia) and ketoprofen (compound of formula Id):



Diclofenac (Ia)



Ketoprofen (Id)

WO 95/30641 discloses a process for the preparation of NO donating analogues of diclofenac. In said process a dihalide derivates is reacted with a salt of the carboxylic acid in DMF. The reaction products were converted into the final products by reaction with $AgNO_3$ in acetonitrile, in accordance with literature reports.

The process of the present invention uses a sulfonated intermediate. This intermediate may be easily manufactured and is highly reactive for reactions with nitrate ions to form -nitrooxyalkyl ester.

In summary, there is a need for a more convenient and more economically efficient process for the manufacturing of large scale quantities of pharmaceutical quality of NO donating compounds, and their sulfonated intermediates, where factors like costs, manufacturing time, use of more environmentally friendly solvents, etcetera are vital for commercial application. The present invention provides for such a process.

## DETAILED DESCRIPTION OF THE INVENTION

The present invention provides for a new process to prepare NO-donating compounds. Further, it provides for new intermediates and a process to prepare said intermediates, especially with regard to large-scale manufacturing.

The new manufacture proccess of NO-donating compounds is described below.

A process for the manufacturing of NO-donating compounds comprising;

$$\underset{\textbf{(I)}}{ML_{T1}A_{T2}\text{-COO}} + \text{HO-X-OH} \xrightarrow[\textbf{Step 1}]{} \underset{\textbf{(II)}}{ML_{T1}A_{T2}\text{-COO-X-OH}}$$

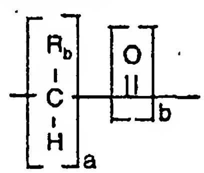
$$\underset{\textbf{(II)}}{ML_{T1}A_{T2}\text{-COO-X-OH}} + RSO_2Cl \xrightarrow[\textbf{Step 2}]{} \underset{\textbf{(III)}}{ML_{T1}A_{T2}\text{-COO-X-O-}SO_2R}$$

$$\underset{\textbf{(III)}}{ML_{T1}A_{T2}\text{-COO-X-O-}SO_2R} + \text{Y-}NO_m \xrightarrow[\textbf{Step 3}]{} \underset{\textbf{(IV)}}{ML_{T1}A_{T2}\text{-COO-X-O-}NO_m}$$

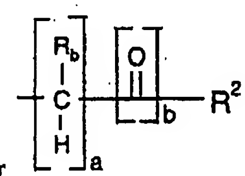
wherein:

M is a radical of a physiologically active compound;

L is O, S, (CO)O, (CO)NH, (CO)$NR^1$, NH, $NR^1$, wherein $R^1$ is a linear or branched alkyl group, or



or



wherein $R_b$ is H, $C_{1-12}$alkyl or $C_{2-12}$alkenyl;

$R^2$ is (CO)NH, (CO)$NR^1$, (CO)O, or $CR^1$ and a and b are independently 0 or 1;

A is a substituted or unsubstituted straight or branched alkyl chain;

X is a carbon linker;

R is selected from the group consisting of $C_1$-$C_8$ alkyl, phenyl, phenylmethyl, $C_1$-$C_4$ alkylphenyl, halophenyl, nitrophenyl, halogen, $CF_3$ and $n$-$C_4F_9$;

Y-$NO_3$ is lithium nitrate, sodium nitrate, potassium nitrate, magnesium nitrate, calcium nitrate, iron nitrate, zink nitrate or tetraalkylammonium nitrate (wherein alkyl is a $C_1$-$C_{18}$-alkyl, which may be straight or branched);

m is 1 or 2; and

T1 and T2 are each independently 0, 1, 2 or 3;

with the proviso that

when $ML_{T1}A_{T2}$-COOH is naproxen then X is not $(CH_2)_4$.

The term "$C_1$-$C_8$ alkyl" means an alkyl having 1 to 8 carbon atoms and includes both straight and branched chain alkyl groups such as methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, t-butyl, etc..

The term "$C_1$-$C_4$ alkylphenyl" means methylphenyl, ethylphenyl n-propylphenyl, i-propylphenyl, n-butylphenyl, i-butylphenyl and t-butylphenyl.

The term "phenylmethyl" means benzyl.

The term "halo" and "halogen" refer to fluoro, chloro or bromo.

The term "halophenyl" and "nitrophenyl" refer to phenyl groups substituted with one or more halogen or nitro group.

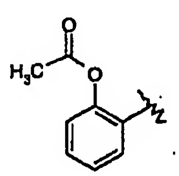
The term "large scale" means a manufacturing scale in the range of "kilogram to multiton".

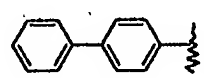
M may be any radical of any physiologically active compound.

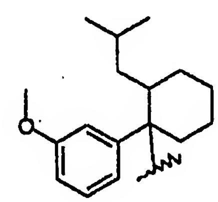
$ML_{T1}A_{T2}$-COOH may be any physiologically active carboxylic acid.

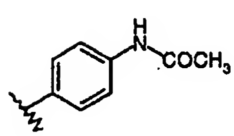
In one embodiment of the invention the group M is an NSAID or COX 1 or 2 inhibitor.

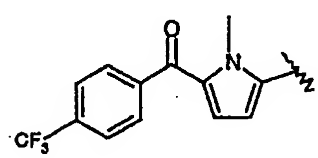
In another embodiment of the invention the group M is selected from the group consisting of











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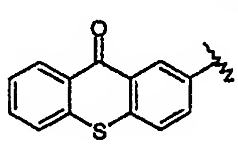
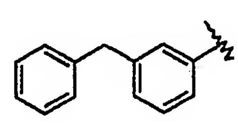
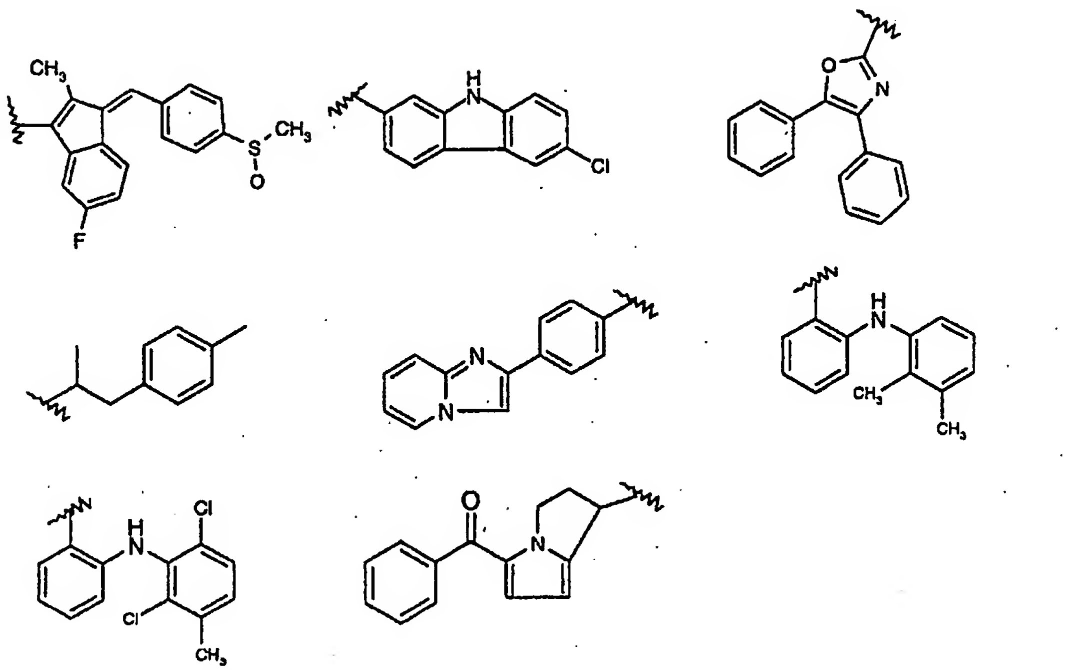


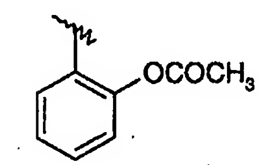


as described in US 3,641,127, and



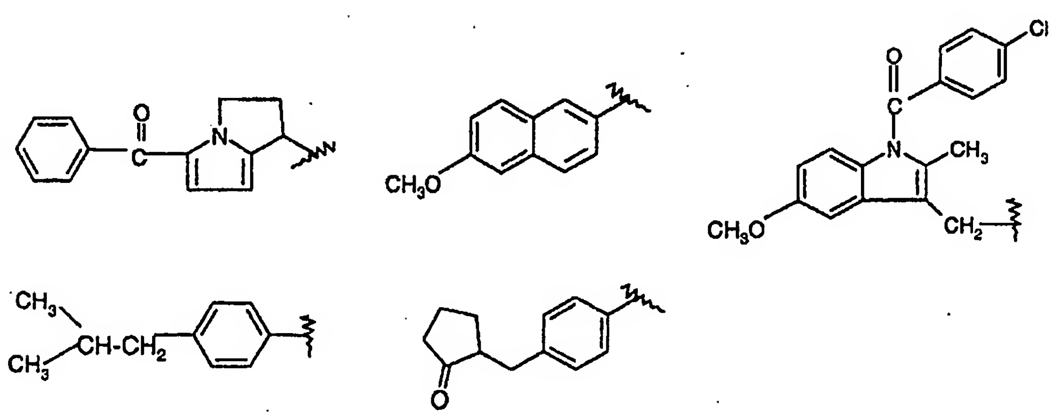
as described in WO 96/32946, and

cycloalkyls as described in WO 98/25918 such as 2,2-dimethyl-cyclopropane-1-methanol, and

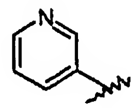


as described in CN 1144092, and

or



as described in WO 95/09831, and



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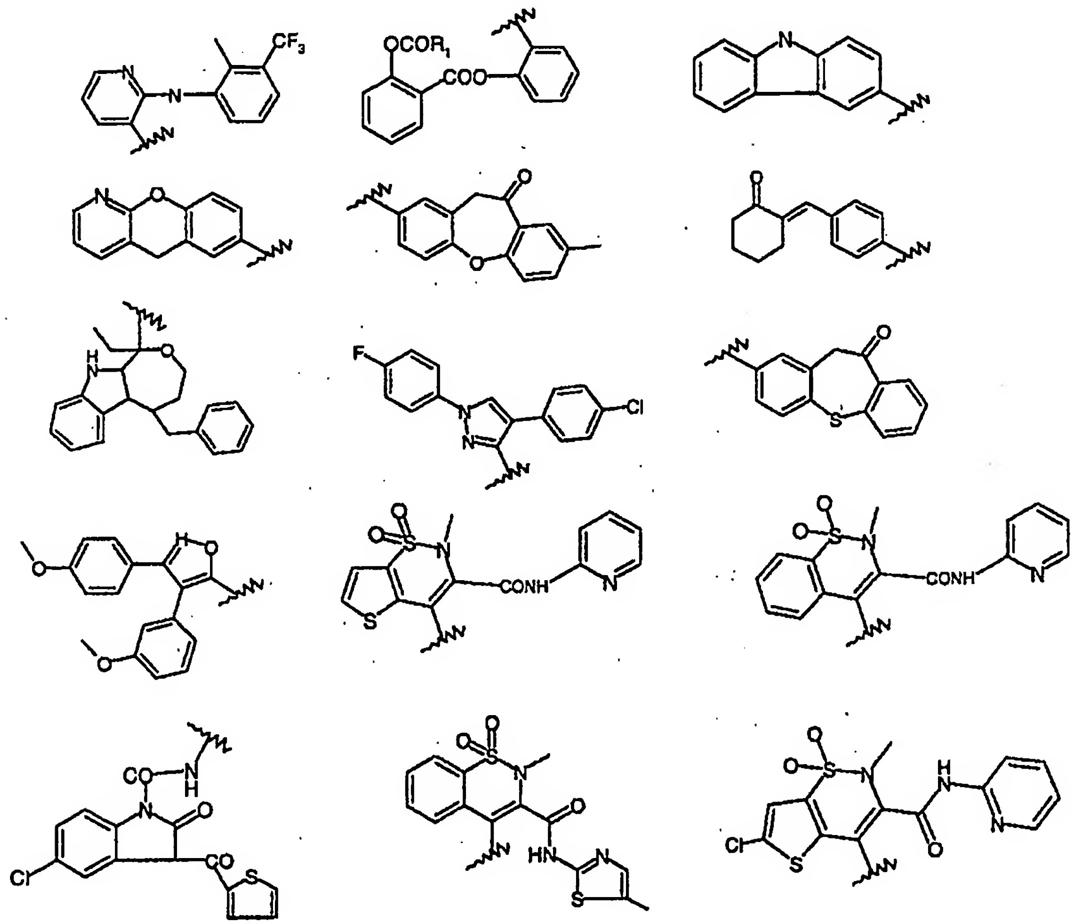

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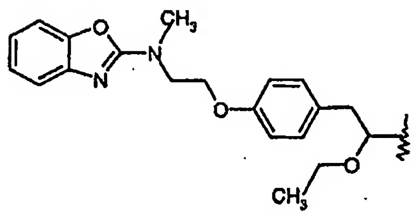
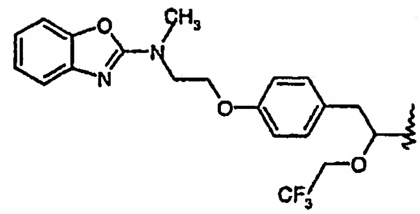
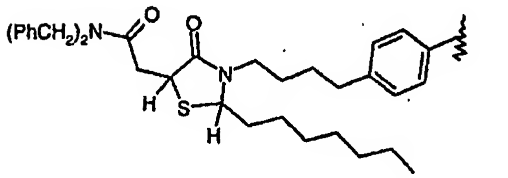
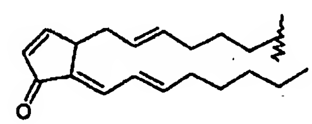
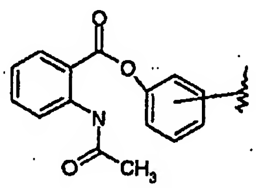
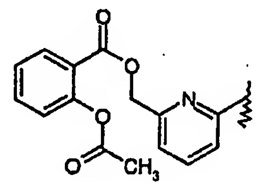


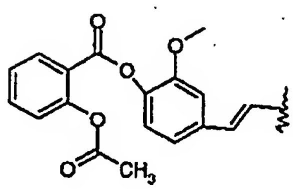


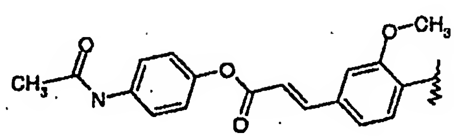


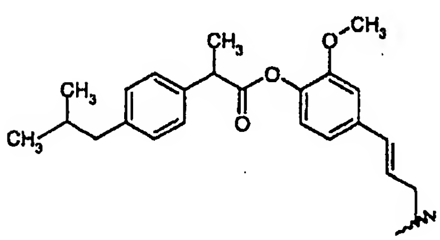


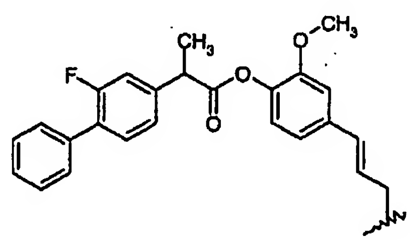




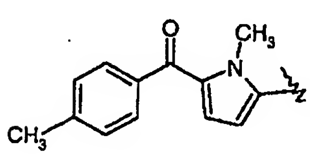


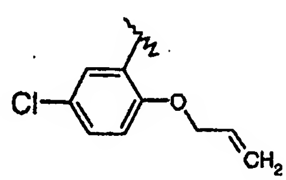


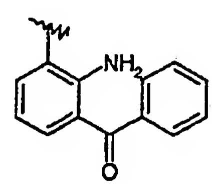


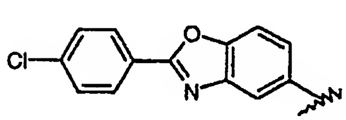


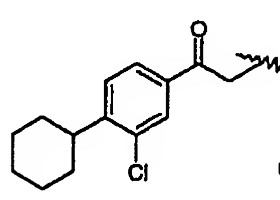
as described in WO 02/30866, and

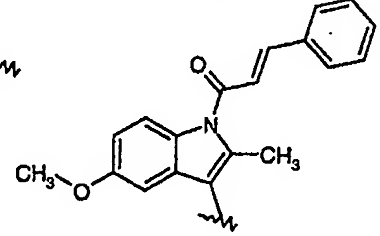


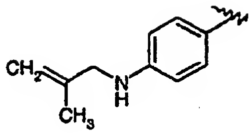
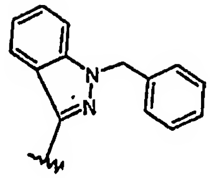
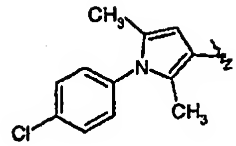
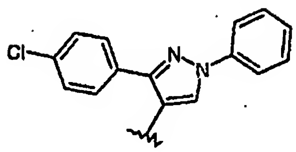
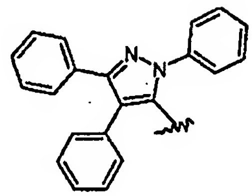
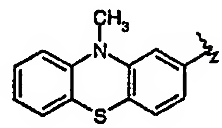
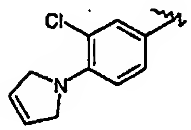
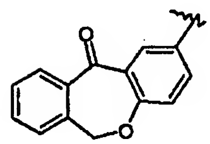
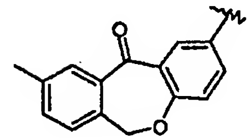
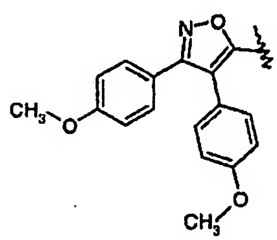
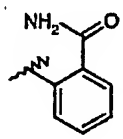
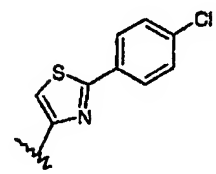
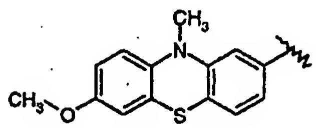
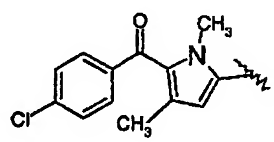
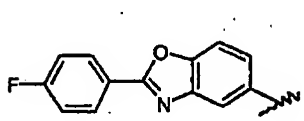
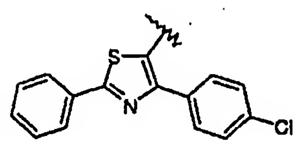
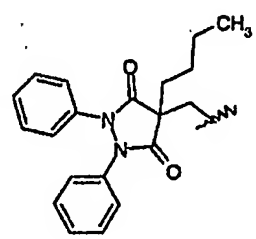
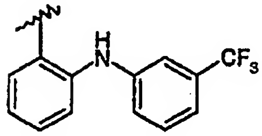
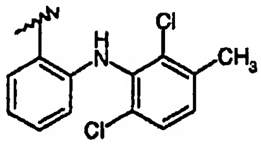
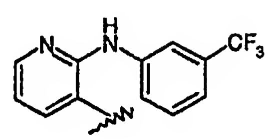


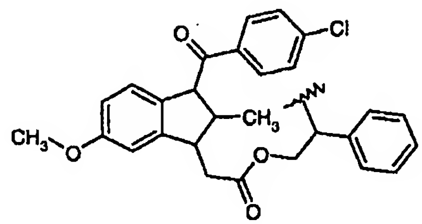


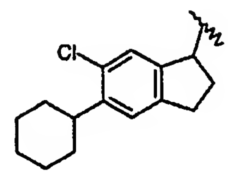


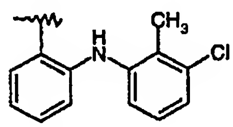


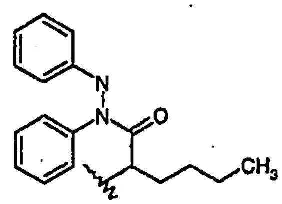




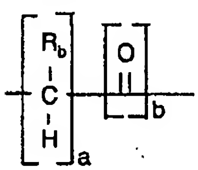




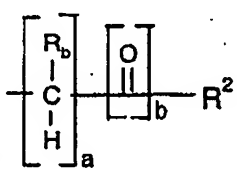


as described in US 6,297260.

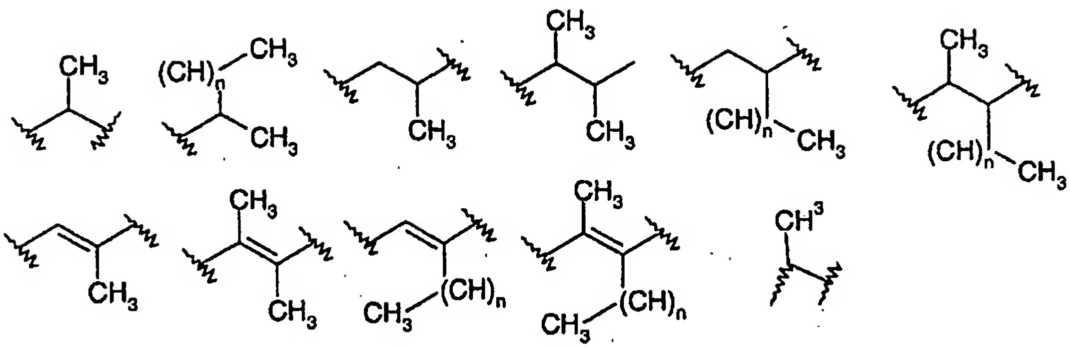
In one embodiment of the invention L is selected from the group consisting of O, S, NH, $NR^1$, wherein $R^1$ is a linear or branched alkyl group, as described in WO 95/09831, and (CO) or (CO)O as described in WO 95/30641, and

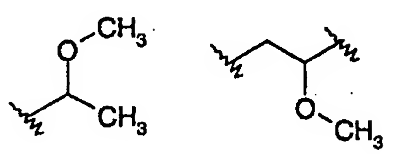


wherein $R_b$ is H, $C_{1-12}$alkyl or $C_{2-12}$alkenyl and a and b are independently 0 or 1, as described in WO 02/053188,

and  wherein $R_b$, a and b are defined as above; and $R^2$ is (CO)NH, $(CO)NR^1$, (CO)O, or $CR^1$.

In another embodiment of the invention A is selected from the group consisting of $-(CH_2)_n-$, n is 0, 1, 2, 3 or 4,





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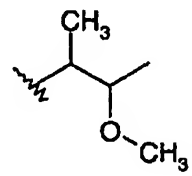
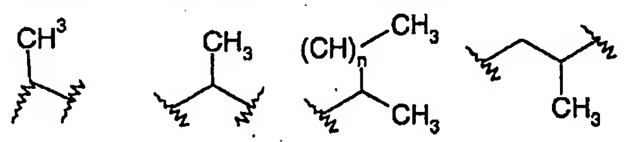
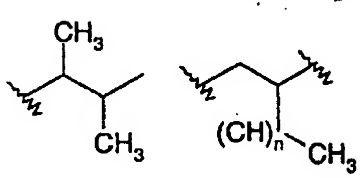


In a further embodiment of the invention A is selected from the group consisting of





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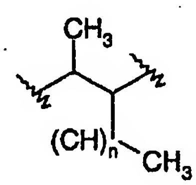
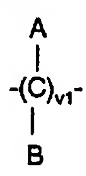


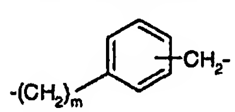
The linker carbon X may be selected from the group consisting of



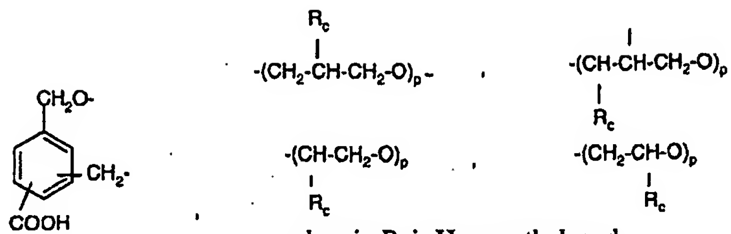
wherein A and B are chosen among hydrogen, linear or branched or cyclic substituted or non substituted alkyl group, and v1 is comprised between 1 and 10

as described in WO 95/09831, and

$-(CH_2\text{-}CH_2\text{-}O)_2-$ , or a cycloalkyl having 5 to 7 carbon atoms optionally substituted and



wherein m is comprised between 0 and 3, and

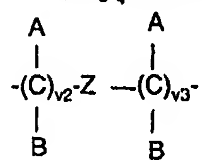


and

wherein $R_c$ is H or methyl, and
p is comprised between 0 and 6,

as described in WO 95/30641 and WO 02/92072, and

$-(CH_2)_q-OCO-(CH_2)_r$, wherein q and r each independently comprise between 0 and 6, and



wherein Z is N, NH, $NCH_3$, O, SO, S or a saturated, unsaturated or aromatic 5 or 6 membered ring or 5 or 6 membered heterocyclic ring containing one or more heteroatoms selected independently from N, O and S, wherein said ring may optionally be substituted,
and v2 and v3 are independently comprised between 0 and 4 and
A, B are defined as hereinabove.

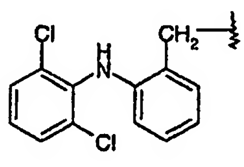
In one embodiment of the invention X is selected from the group consisting of linear, branched or cyclic $-(CH_2)-_{w1}$ wherein w1 is an integer of from 2 to 10; $-(CH_2)_{w2}-O-(CH_2)_{w3}-$ wherein w2 and w3 are integers of from 2 to 10; and $-CH_2-C_6H_4-CH_2-$.

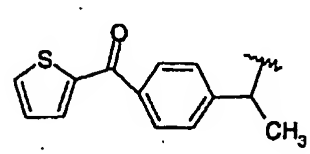
In another embodiment of the invention X is selected from the group consisting of linear $-(CH_2)_{w1}-$ wherein w1 is an integer of from 2 to 6;

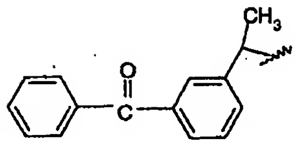
$-(CH_2)_2-O-(CH_2)_2-$ and $-CH_2-C_6H_4-CH_2-$.

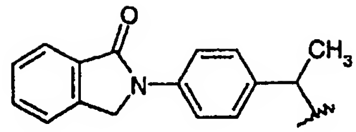
In a further embodiment of the invention R is selected from the group consisting of $C_1$-$C_8$ alkyl, phenyl, phenylmethyl, $C_1$-$C_4$ alkylphenyl, halophenyl, nitrophenyl and halogen;

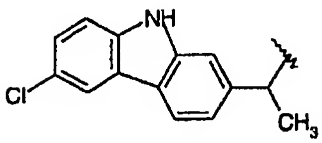
In one embodiment of the invention the group $ML_{T1}A_{T2}$ is selected from the group consisting of

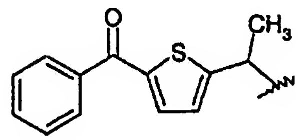


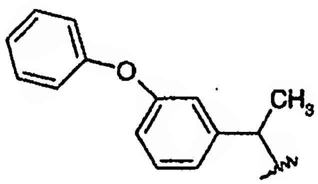


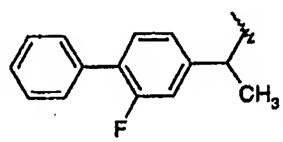


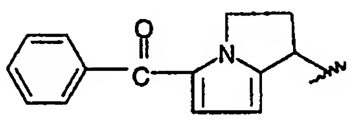


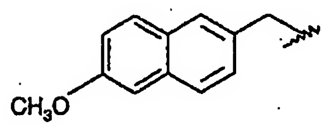


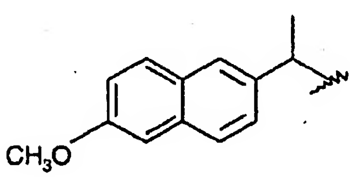


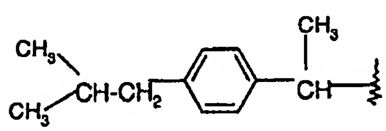


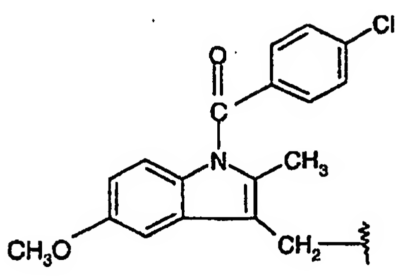




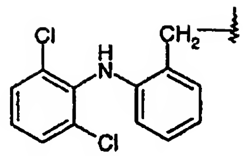


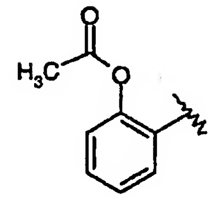


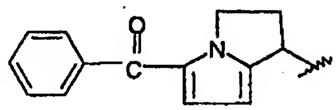


and  .

In another embodiment of the invention the group $ML_{T1}A_{T2}$ is selected from the group consisting of







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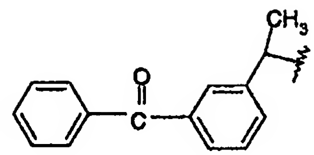

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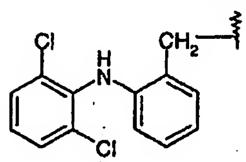
In a particular embodiment the group $ML_{T1}A_{T2}$ is



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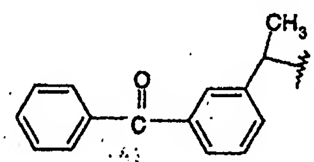

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**Step 1**

$$ML_{T1}A_{T2}\text{-COOH} + \text{HO-X-OH} \longrightarrow ML_{T1}A_{T2}\text{-COO-X-OH}$$

(I) (II)

wherein M, L, A, T1 , T2 and X are as defined above.

$ML_{T1}A_{T2}$-COOH may be esterified in reaction step 1 by using acid catalysed esterfication in the presence of diethylene glycol as described in DE 88-3811118 where p-toluenesulfonic acid is used.

The esterification step 1 may be performed in a manner known to a person skilled in the art, for example by treating the compound of formula I, for example diclofenac, and diethylene glycol with an acidic or dehydrating agent.

One embodiment relates to the process of the invention whereby an acidic or dehydrating agent in step 1 is selected from the group consisting of sulphuric acid or its salts, perchloric acid (e.g. 70%) or other suitable acids such as polystyrene sulphonic acids, zeolites, acidic clays, sand in combination with strong hydrophilic acids such as perchloric acid or gaseous hydrogen chloride and montmorillonites.

Compounds of formula II may also be prepared in the same manner using 1,4-butandiol, 1,3-propandiol and triethyleneglycol respectively. In ES 85-548226 thionyl chloride is used to catalyse the esterfication.

The acids may be used in the gas, fluid or solid form. The solid heterogeneous acids can relatively easily be filtered from the reaction solution and re-used in large-scale production processes.

Examples of other coupling reagents useful for the esterification step 1 are carbodiimides such as *N,N´*-dicyclohexylcarbodiimide (DCC), acid chlorides such as oxalyl chloride, chloroformates such as isobutyl chloroformate or other reagents such as cyanuric chloride, *N,N´*-carbonyldiimidazole, diethyl chlorophosphite, 2-chloro-1-methyl-pyridinium iodide and 2,2´-dipyridyl disulphide.

One embodiment relates to the process of the invention whereby the solvent in step 1 is a non-polar and/or non acidic solvent.
The reaction step 1 may be performed in a solvent selected from the group comprising of aromatic hydrocarbons such as benzene or toluene, aliphatic hydrocarbons such as n-heptane, ketones such as methyl isobutylketone, ethers such as tetrahydrofuran or diethyleneglycol dimethyl ether and chlorinated hydrocarbons such as dichloromethane or chlorobenzene, or mixtures thereof.
Alternatively, an excess of the corresponding diol may be used as solvent optionally mixed with any of the other organic solvents mentioned above.

Compounds of formula II as obtained in step 1 may be purified by way of extraction, batch-wise or continuously, to obtain a solution comprising the compound of formula II having a chromatographic purity of at least 92% and preferably more than 97% (after extraxtion step i) and an alkylene diol or alkylene glycol content below about 0.5% (w/w) (after extraction step ii).

*Extraction step i)*

In this extraction step the chromatographic purity is improved. The solution used in this extraction step may comprise a mixture of i) alkylene diol or alkylene glycol, ii) water

and/or a low molecular weight aliphatic alcohol and iii) a hydrocarbon solvent or mixtures thereof or mixtures of organic solvents with hydrocarbon solvents.

The low molecular weight aliphatic alcohols may be selected from the group consisting of methanol, ethanol and propanol, or mixtures thereof.

The hydrocarbon solvents used for extraction step i) may be selected from the group comprising of toluene, cumene, xylenes, ligroin, petroleum ether, halobenzenes, heptanes, hexanes, octanes, cyclohexanes, cycloheptanes, and the like, or mixtures thereof.

Suitable organic solvents used for extraction step i) may be selected from the groups comprising of ketones such as methyl *iso*-butyl ketone, ethers such as di-*n*-butyl ether or *tert*-butyl methyl ether and aliphatic esters such as ethyl acetate or *n*-butyl acetate and haloalkanes such as dichloromethane, or mixtures thereof.

The purified compound of formula II is obtained as a solution in a mixture of alkylene diol or alkylene glycol with water and/or a low molecular weight aliphatic alcohol.

*Extraction step ii)*

This extraction is performed to lower the alkylene diol or alkylene glycol-content and performed after extraction step i) wherein the chromatographic purity is improved as described above. The solution may comprise i) a mixture of water and/or a low molecular weight aliphatic alcohol and ii) an organic solvent or mixtures of organic solvents.

The low molecular weight aliphatic alcohols may be selected from the group consisting of methanol, ethanol and propanol, or mixtures thereof.

A suitable organic solvent used for extraction step ii) may be selected from the groups comprising of aromatic hydrocarbons such as toluene, cumene or xylenes, ketones such as methyl *iso*-butyl ketone, ethers such as di-*n*-butyl ether or *tert*-butyl methyl ether and aliphatic esters such as ethyl acetate or *n*-butyl acetate and haloalkanes such as dichloromethane, or mixtures thereof.

The total amount of solvents used in the esterification process step **1**, may vary between 0 to 100 volume parts per weight of starting material.

The temperature of the esterification step **1** may be between -100°C to +130°C, preferably between 0°C and +120°C.

**Step 2**

$$ML_{T1}A_{T2}\text{-COO-X-OH} + RSO_2Cl \longrightarrow ML_{T1}A_{T2}\text{-COO-X-OSO}_2R,$$

(II) (III)

wherein:

M, L, A, T1, T2, X and R are as defined above.

The reaction condition in step 2 would suitably involve an excess of $RSO_2Cl$ in an organic solvent or a mixture of organic solvents.
A suitable solvent in step 2 may be selected from the groups comprising of aromatic hydrocarbons such as toluene, cumene or xylenes, ketones such as methyl *iso*-butyl ketone, ethers such as di-*n*-butyl ether, *tert*-butyl methyl ether or tetrahydrofuran, aliphatic nitriles such as acetonitrile and aliphatic esters such as ethyl acetate or *n*-butyl acetate and haloalkanes such as dichloromethane, or mixtures thereof.
One embodiment relates to the process of the invention whereby the solvents in step 2 are selected from a group consisting of toluene, cumene, xylenes, ethyl acetate, acetonitrile, butyl acetate and isopropyl acetate.

A base may be added in step 2. In one embodiment of the invention the base in step 2 may be selected from the group consisting of triethylamine, pyridine, *N*-methylmorpholine, diisopropylethylamine, tributylamine and *N*-methyl-piperidine.
Another embodiment relates to the process of the invention whereby the base in step 2 is triethylamine or *N*-methylmorpholine.

A further embodiment relates to the process of the invention whereby a catalyst such as 4-(dimethylamino)pyridine may optionally be used in step 2.

Compounds of formula III as obtained in step 2 may be purified by crystallisation from an organic solvent, optionally using a hydrocarbon as antisolvent to obtain a crystalline solid having a purity of about 95% and particularly about 98%.

One embodiment relates to the process of the invention whereby the compound of formula III in step 2 is crystallized from an organic solvent, optionally using an antisolvent to obtain a crystalline solid having a purity of at least 95%.

In another embodiment of the invention the solvent used for the crystallisation may be selected from the group comprising of aromatic hydrocarbons such as toluene, cumene or xylenes, ketones such as methyl iso-butyl ketone, ethers such as di-n-butyl ether, tert-butyl methyl ether or tetrahydrofuran, aliphatic nitriles such as acetonitrile and aliphatic esters such as ethyl acetate or butyl acetate, or mixtures thereof.

A further embodiment relates to the process of the invention whereby the solvent used for the crystallisation in step 2 is selected from the group consisting of toluene, cumene, xylenes, ethyl acetate, acetonitrile, butyl acetate and isopropyl acetate, or mixtures thereof.

Yet another embodiment relates to the process of the invention whereby the antisolvent used for the crystallisation in step 2 is selected from the group comprising of ligroin, petroleum ether, halobenzenes, heptanes, hexanes, octanes such as isooctane, cyclohexanes, cycloheptanes and alcohols, or mixtures thereof.

**Step 3**

$$\underset{(III)}{ML_{T1}A_{T2}\text{-COO-X-OSO}_2R} + Y\text{-NO}_3 \longrightarrow \underset{(IV)}{ML_{T1}A_{T2}\text{-COO-X-ONO}_2}$$

wherein M, L, A, T1, T2, X, R and Y are as defined above.

In step 3 of the manufacturing process, a compound of formula IV is obtained by reacting the compound of formula III with a nitrate source ($Y\text{-NO}_3$) optionally in the presence of a solvent.

This reaction may be performed with a nitrate source $Y\text{-NO}_3$ selected from the group consisting of lithium nitrate, sodium nitrate, potassium nitrate, magnesium nitrate, calcium nitrate, iron nitrate, zink nitrate and tetraalkylammonium nitrate (wherein alkyl is a $C_1$-$C_{18}$-alkyl, which may be straight or branched).

One embodiment relates to the process of the invention whereby the nitrate sources Y-$NO_3$ in step 3 is selected from the group consisting of lithium nitrate, sodium nitrate, potassium nitrate, magnesium nitrate and calcium nitrate, or mixtures thereof.

Another embodiment relates to the process of the invention whereby the organic solvent in step 3 is a polar aprotic solvent.
In a further embodiment of the invention the polar aprotic solvents used in step 3 may be selected from the group comprising of *N*-methylpyrrolidinone, *N,N*-dimethylacetamide, sulpholane, tetramethylurea, 1,3-dimethyl-2-imidazolidinone and nitriles such as acetonitrile, or mixtures thereof.
Other solvents may be aromatic hydrocarbons such as toluene, aliphatic hydrocarbons such as n-heptane, ketones such as methyl ethyl ketone, methyl isobutylketone, ethers such as tetrahydrofuran or diethyleneglycol dimethyl ether, chlorinated hydrocarbons such as chlorobenzene, aliphatic esters such as ethyl acetate, butyl acetate or isopropyl acetate, nitrated hydrocarbons such as nitromethane, ethylene glycols such as polyethylene glycol and mixtures of these, optionally with an added aliphatic alcohols such as methanol, ethanol, n-propanol, i-propanol, n-butanol, i-butanol or t-butanol.

The nitration step 3 may also be performed in water, optionally in combination with any of the above listed organic solvents.

The nitration step 3 may optionally be performed in the presence of a phase-transfer-catalyst.
One embodiment relates to the process of the invention whereby the phase transfer-catalyst in step 3 is selected from the group consisting of tetraalkylammonium salt, arylalkylammonium salt, tetraalkylphosphonium salt, arylalkylphosphonium salt, crown ether, pentaethylene glycol, hexaethylene glycol and polyethylene glycols, or mixtures thereof.

Compounds of formula IV as obtained in step 3 may be purified by crystallisation from an organic solvent optionally using hydrocarbons, alcohols or water as anti solvent to obtain a crystalline solid product of a purity of 90% and particularly about 95%.

One embodiment relates to the process of the invention whereby the compound of formula IV in step **3** is extracted batch-wise or continuosly and crystallized from an organic solvent optionally using an anti solvent to obtain a crystalline solid having a purity of at least 95%.

Suitable solvents used for the crystallisation in step **3** may be selected from the group comprising of lower alkyl acetates e.g. linear or branched $C_{1-6}$ alkyl acetates such as ethyl acetate, *iso*-propyl acetate or butyl acetate, lower linear or branched $C_{2-6}$ alkyl alcohols, preferably $C_{2-4}$ alkyl alcohols such as ethanol or *iso*-propanol, aliphatic and aromatic hydrocarbons e.g. $C_{5-12}$ aliphatic hydrocarbons or $C_{6-10}$ aromatic hydrocarbons such as isooctane, cumene, xylenes, *n*-heptane, 1-methyl-2-pyrrolidinone or toluene, dialkyl ketones e.g. di-$C_{1-6}$ alkyl ketones such as acetone, methyl ethyl ketone, methyl *iso*-butyl ketone or 4-methyl-2-pentanone, dialkyl ethers e.g. di-$C_{1-6}$ alkyl ethers such as di-*iso*-propyl ether, di-n-butyl ether, *tert*-butyl methyleter or tetrahydrofuran, aliphatic nitriles such as acetonitrile or 1-methyl-2-pyrrolidinone and water, or mixtures thereof.
One embodiment relates to the process of the invention whereby the solvent used for the crystallisation in step **3** is selected form the group consisting of butylacetate, isooctane, acetone and water, or mixtures thereof.
In another embodiment of the invention the antisolvent used for the crystallisation in step **3** may be selected from the group comprising of lower alcohols such as ethanol or 2-propanol, toluene, cumene, xylenes, ligroin, petroleum ether, halobenzenes, heptanes, hexanes, octanes, cyclohexanes and cycloheptanes, or mixtures thereof.
A further embodiment relates to the process of the invention whereby the anti solvent used for the crystallisation in step **3** is selected from the group consisting of 2-propanol, isooctane, heptane and water, or mixtures thereof.

The temperature used in process step **1** and **2** may be between -100°C to +130°C. The temperature is particularly kept below 130 °C, because the stability of the end product might be affected by a high temperature. Reaction step **3** is particularly performed at a temperature below 90°C. The temperature used in the crystallization steps may be below 0°C, for example down to -40°C.

Another embodiment relates to the process of the invention whereby the temperature is between -40°C and 120°C.
Room temperature shall mean a temperature between 18°C and 25°C.

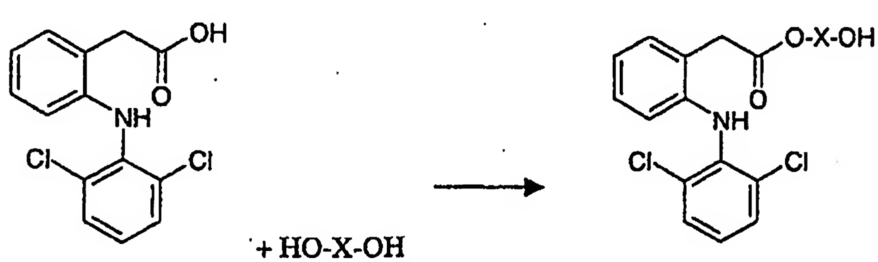
The total amount of solvents may vary between 0 to 100 volume parts per weight of starting material.

The skilled person will appreciate that the different reaction steps need different reaction times.

In the process of the present invention the use of explosive intermediates such as nitrooxyalkanols are avoided. Furthermore, the new process is commercially and environmentally more advantageous than the known processes.

Another advantage of the process of the present invention is that the enantiomeric purity of the starting material is at least maintained in the end products (IV) for which asymmetric carbons are present.

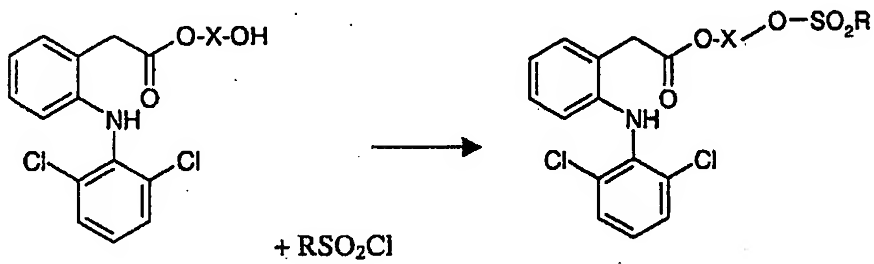
One embodiment of the invention relates to a process for the manufacturing of NO donating diclofenac of formula IVa, IVb and IVc, comprising:
step 1, reacting a compound of formula Ia with HO-X-OH, wherein X is $C_2H_4OC_2H_4$, $C_4H_8$ or $C_2H_4OC_2H_4OC_2H_4$, to obtain compounds of formula IIa, IIb or IIc,




diclofenac (Ia) II,

followed by,

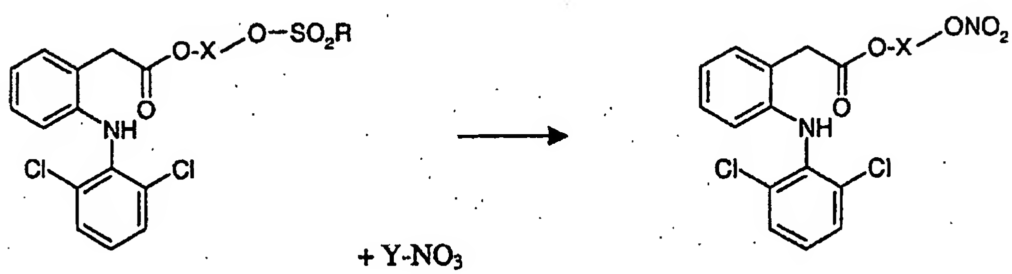
step **2**, reacting the compounds of formula IIa, IIb or IIc with $RSO_2Cl$, wherein R is as defined above, to obtain compounds of formula IIIa, IIIb or IIIc,




II III,

and

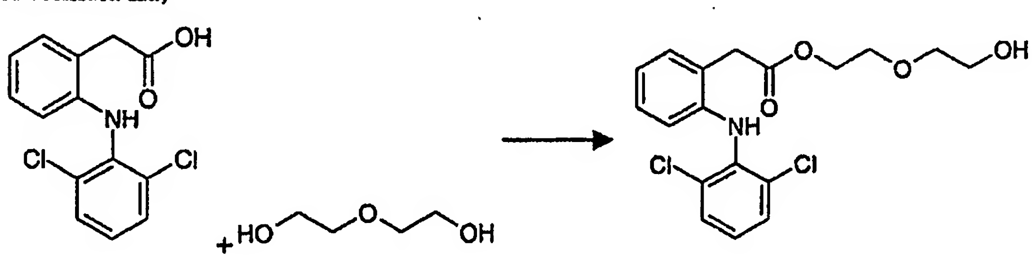
step **3**, reacting the compounds of formula IIIa, IIIb or IIIc with a nitrate source $Y\text{-}NO_3$ is as defined above, to obtain compounds of formula IVa, IVb or IVc,




III IV.

Another embodiment of the invention relates to a process for the manufacturing of NO donating diclofenac of formula IVa comprising:

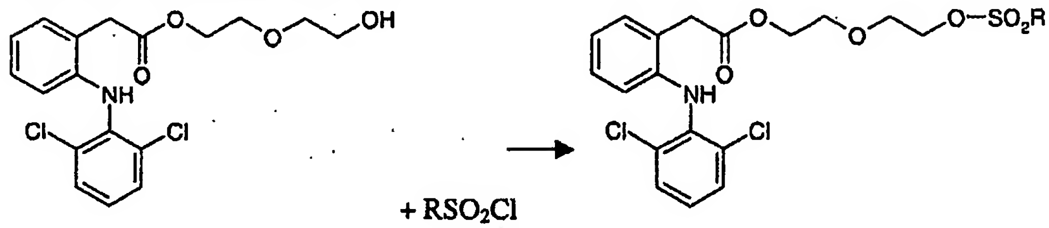
step **1**, reacting the compound of formula Ia with diethylene glycol to obtain a compound of formula IIa,




Ia IIa

followed by,

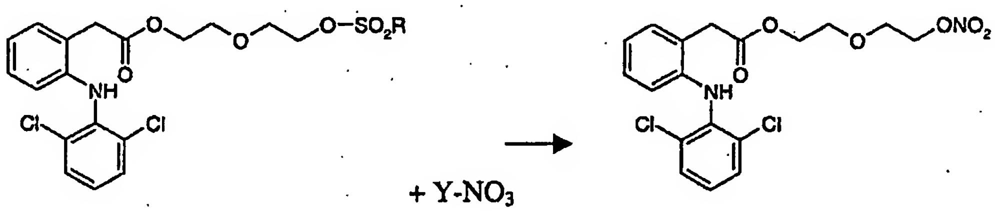
step 2, reacting the compound of formula IIa with $RSO_2Cl$, wherein R is as defined above, to obtain a compound of formula IIIa,



+ $RSO_2Cl$

IIa IIIa

step 3, reacting the compound of formula IIIa with a nitrate source $Y\text{-}NO_3$ as defined above, to obtain a compound of formula IVa,

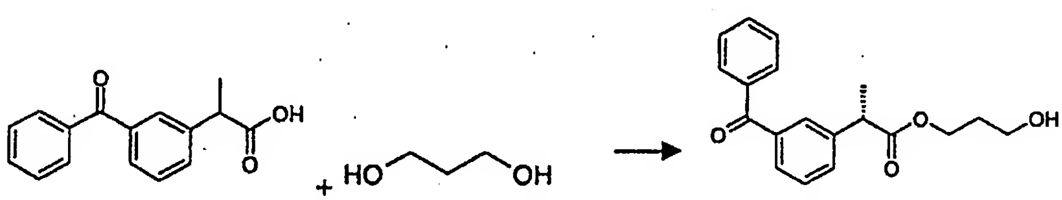


+ $Y\text{-}NO_3$

IIIa IVa.

Another embodiment of the invention relates to a process for the manufacturing of NO donating ketoprofen of formula IVd comprising:

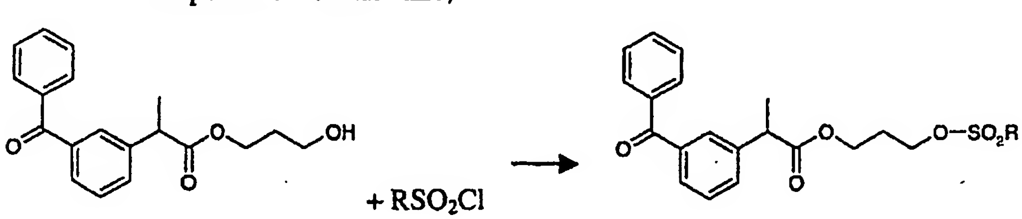
step 1, reacting a compound of formula Id with 1,3-propanediol to obtain a compound of formula IId,



Id IId

followed by,

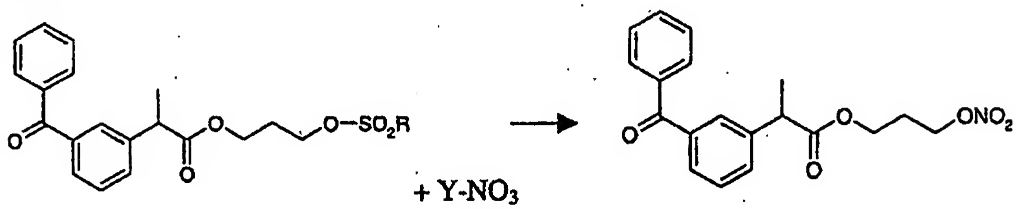
step 2, reacting the compound of formula IId with $RSO_2Cl$, wherein R is as defined above, to obtain a compound of formula IIId,



+ $RSO_2Cl$

IId IIId

step 3, reacting the compound of formula IIId with a nitrate source Y-$NO_3$ as defined above, to obtain a compound of formula IVd,

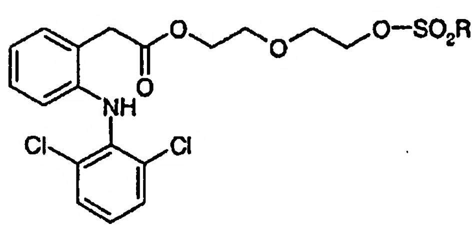


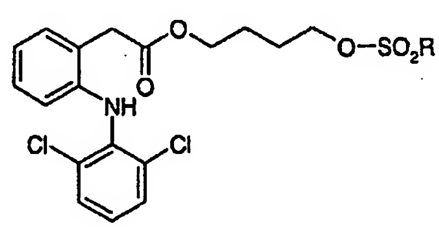

IIId IVd.

One embodiment of the invention relates to a process as described above for the manufacturing of the *S*-enantiomer of NO donating ketoprofen of formula IVd.

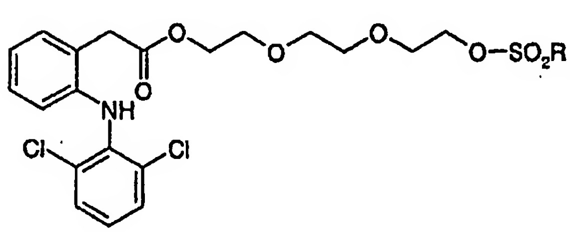
Another embodiment of the invention relates to intermediates of formula III, $ML_{T1}A_{T2}$-X-O-$SO_2$R, wherein M, L, A, T1, T2, X and R are as defined above.

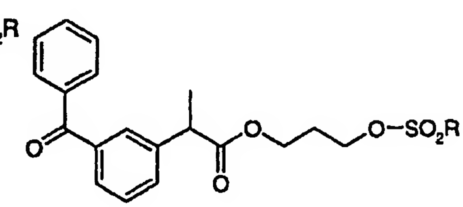
A further embodiment of the invention relates to compounds of formula IIIa, IIIb, IIIc and IIId:




IIIa IIIb

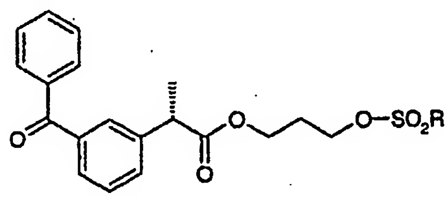



IIIc IIId

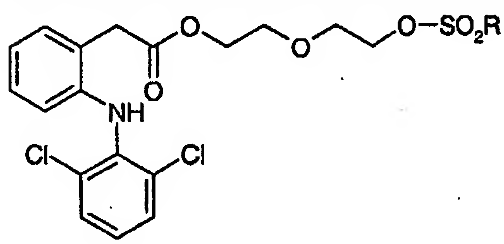
wherein R is selected from the group consisting of $C_1$-$C_8$ alkyl, phenyl, phenylmethyl, $C_1$-$C_4$ alkylphenyl, halophenyl, nitrophenyl, halogen, $CF_3$ and $n$-$C_4F_9$.

Yet another embodiment of the invention relates to the *S*-enantiomer of the compound of formula IIId



wherein R is selected from the group consisting of $C_1$-$C_8$ alkyl, phenyl, phenylmethyl, $C_1$-$C_4$ alkylphenyl, halophenyl, nitrophenyl, halogen, $CF_3$ and $n$-$C_4F_9$.

Yet a further embodiment of the invention relates to compounds of formula IIIa,



IIIa

wherein R is selected from the group consisting of $C_1$-$C_8$ alkyl, phenyl, phenylmethyl, $C_1$-$C_4$ alkylphenyl, halophenyl, nitrophenyl, halogen, $CF_3$ and $n$-$C_4F_9$.

One object of the present invention relates to the use of the compounds of formula III, $ML_{T1}A_{T2}$-X-O-$SO_2$R, wherein M, L, A, T1, T2, X and R are as defined above, as an intermediate for the manufacturing of a pharmaceutically active compound.

Another object of the present invention relates to the use of the compounds of formula IIIa, IIIb, IIIc and IIId as defined above, as an intermediate for the manufacturing of 2-[2-(nitrooxy)ethoxy]ethyl {2-[(2,6-dichlorophenyl)amino]phenyl}acetate, 4-(nitrooxy)butyl {2-[(2,6-dichlorophenyl)amino]phenyl}acetate, 2-{2-[2-(nitrooxy)ethoxy]ethoxy}ethyl {2-

[(2,6-dichlorophenyl)amino]phenyl}acetate, 3-(nitrooxy)propyl 2-(2-benzoylphenyl)-propanoate and 3-(nitrooxy)propyl (2*S*)-2-(2-benzoylphenyl)propanoate.

Yet another object of the present invention relates to the use of intermediate compounds of formula IIIa, IIIb, IIIc and IIId as defined above, prepared according to the process described above under step **1** and **2**, for the manufacturing of a medicament for the treatment of pain and inflammation.

One embodiment of the invention related to the use of the process as defined above for the large scale manufacturing of NO donating compounds of formula IV.
Another embodiment of the invention related to the use of the process as defined above for the large scale manufacturing of the compounds of formula IVa, IVb, IVc and IVd.

## Examples

The present invention is described in more detail in the following non-limiting examples.

*Synthesis of 2-[2-(nitrooxy)ethoxy]ethyl {2-[(2,6-dichlorophenyl)amino]phenyl}acetate (compound of formula IVa).*

2-(2-hydroxyethoxy)ethyl {2-[(2,6-dichlorophenyl)amino]phenyl}acetate (compound of formula IIa).

Diclofenac sodium (20 g, 63 mmol) was dissolved in diehyleneglycol (67 g, 0.63 mol) at 60°C. Toluene (170 mL) and conc. sulfuric acid (4.5 mL, 81.7 mmol) were added after the solids had dissolved. The reaction mixture was heated at 60°C for 14 h before addition of $K_2CO_3$ (1 M, 120 mL). After phase separation the aqueous phase was discarded and the organic phase was washed with water (100 mL). The organic phase was concentrated under vacuum to give 23 g of IIa as a brown oil (85 % yield, 90 %-area HPLC-purity).MS [$M^+$]=384; $^1$H-NMR ($CDCl_3$) δ 7.34 (app d, *J* = 8 Hz, 2H), 7.24 (app d, *J* = 8 Hz, 1H), 7.12 (app t, *J* = 7 Hz, 1H), 6.92-7.05 (m, 2H), 6.88 (br s, 1H), 6.54 (app d, *J* = 8 Hz, 1H), 4.32 (app t, *J* = 4 Hz, 2H), 3.85 (s, 2H), 3.64-3.76 (m, 4H), 3.50-3.58 (m, 2H), 2.08 (br s,

1H); $^{13}$C-NMR ($CDCl_3$) δ 172. 8, 143.1, 138.2, 131.1, 129.9, 129.4, 128.5, 124.6, 124.5, 123.5, 122.4, 118.7, 72.8, 69.3, 64.7, 62.10, 53.9, 38.9.

2-{2-[(methylsulfonyl)oxy]ethoxy}ethyl {2-[(2,6-dichlorophenyl)amino]phenyl}acetate (compound of formula IIIa).

The hydroxiester IIa (23 g, 0.16 mol) isolated in the previous step was dissolved in toluene (300 mL) and *N*-methyl morpholine (16.9 g, 157 mmol) at 30°C. Methanesulfonyl chloride (18.0 g, 157 mmol) dissolved in toluene (50 mL) was added drop wise to the reaction. The reaction was heated to 60°C over 2h after which the reaction mixture was washed with 0.1 M sulfuric acid (200 mL) and water (2 x 200 mL). The organic phase was concentrated under reduced pressure and the resulting oil was dissolved in toluene (200 mL) and concentrated again. The crude product was dissolved in toluene (150 mL) at 30°C and isooctane (150 mL) was added over 1h before cooling to 5°C. After stirring the resulting slurry over night the crystals were filtered off, washed with isooctane (100 mL) and then dried at 40°C under vacuum. This gave 52.4 g (71 %) of the title compound as white crystals (98.0 %-area HPLC-purity). Mp = 87°C; MS [$M^+$] = 462; $^1$H-NMR ($CDCl_3$) δ 7.34 (app d, $J$ = 8 Hz, 2H), 7.23 (app d, $J$ = 7 Hz, 1H), 7.13 (app t, $J$ = 7 Hz, 1H), 6.97 (app q, $J$ = 8 Hz, 2H), 6.85 (br s, 1H), 6.54 (app d, $J$ = 8 Hz, 1H), 4.26-4.36 (m, 4H), 3.84 (s, 2H), 3.68-3.78 (m, 4H), 2.99 (s, 3H); $^{13}$C-NMR ($CDCl_3$) δ 172.2, 142.7, 137.7, 130.9, 129.5, 128.9, 128.1, 124.2, 124.1, 122.1, 118.3, 100.0, 69.1, 69.0, 64.1, 38.5, 37.6.

2-[2-(Nitrooxy)ethoxy]ethyl {2-[(2,6-dichlorophenyl)amino]phenyl}acetate (compound of formula IVa).

The mesylate IIIa (461 g, 0.997 mol) and lithium nitrate (293 g, 4.25 mol) were dissolved in *N*-methyl pyrrolidinone (1800 mL) and the temperature was set to 75°C. After 3.5 h another portion of lithium nitrate (146 g, 2.11 mol) was added. The reaction was run over night (total 27 h) before the reaction was stopped by decreasing to 35°C and addition of toluene (1800 mL) and water (1000 mL). The water phase was separated off and the organic phase was washed with water (1000 mL). The organic phase was evaporated to dryness giving 513 g of IVa which solidified upon standing. An analytical sample (10 g) was recrystallised from n-butylacetate (30 mL) and isooctane (60 mL). Mp = 73°C; MS [$M^+$] = 429; $^1$H-NMR ($CDCl_3$) δ 7.34 (app d, $J$ = 8, 2H) 7.24 (app d, $J$ = 8 Hz, 1H), 7.12

(app t, $J$ = 8 Hz, 1H), 6.97 (app q, $J$ = 8 Hz, 2H), 6.86 (br s, 1H), 6.55 (d, J = 8 Hz, 1H), 4.54 (t, $J$ = 4 Hz, 2H), 4.30 (t, $J$ = 5 Hz, 2H), 3.84 (s, 2H), 3.66-3.74 (m, 4H); $^{13}$C-NMR ($CDCl_3$) δ 171. 7, 142.2, 137.2, 130.4, 129.0, 128.4, 127.5, 123.7, 123.6, 121.5, 117.7, 71.4, 68.7, 66.6, 63.6, 38.0

*Synthesis of 4-(nitrooxy)butyl {2-[(2,6-dichlorophenyl)amino]phenyl}acetate (compound of formula IVb)*

<u>4-Hydroxybutyl {2-[(2,6-dichlorophenyl)amino]phenyl}acetate (compound of formula IIb).</u>

To a mixture of Diclofenac sodium (20.0 g, 62.9 mmol) and 1,4-butanediol (56.6 g, 629 mmol) in toluene (120 mL) at 65 °C was added sulfuric acid (4.5 mL, 84.5 mmol). The resulting clear solution was stirred at 65 °C over 6 h before cooling to 50 °C. The reaction mixture was washed with aqueous potassium bicarbonate (0.2 M, 120 mL) and water (2 x 120 mL). After phase separation the toluene was evaporated giving 22.9 g IIa as a brown oil (88 %, HPLC purity of at least 89 %-area), which was used in the next step. $^{1}$H-NMR ($CDCl_3$) δ 7.34 (app d $J$ = 8 Hz, 2H), 7.23 (app d, $J$ = 8 Hz, 1H), 7.13 (app t, $J$ = 7 Hz, 1H), 6.97 (app q, $J$ = 8 Hz, 2H), 6.56 (app d, $J$ = 8 Hz, 1H), 4.19 (t, $J$ = 7 Hz, 2H), 3.82 (s, 2H), 3.63 (t, $J$ = 7Hz, 2H), 1.71-1.80 (m, 2 H), 1.55-1.64 (m, 2H); $^{13}$C-NMR ($CDCl_3$) δ 172.4, 142.6, 137.7, 130.8, 129.4, 128.8, 127.9, 124.4, 124.0, 121.9, 118.2, 65.1, 62.1, 38.6, 28.9, 25.0.

<u>4-[(Methylsulfonyl)oxy]butyl {2-[(2,6-dichlorophenyl)amino]phenyl}acetate (compound of formula IIIb).</u>

The ester IIb (20 g, 54 mmol) from the previous step and methanesulfonyl chloride (7.5 g, 65.1 mmol) were dissolved in toluene (100 mL) at 20 °C. *N*-Methylmorpholine (6.0 g, 59.7 mmol) was added drop wise. After complete addition the solution (slightly cloudy) was heated at 40 °C over 5 h. Toluene was added (40 mL) and the reaction was heated at 60 °C for 0.5 h before addition of sulfuric acid (aq) (0.1 M, 80 mL). The aqueous layer was discarded and the toluene phase was washed with aqueous potassium carbonate (0.6 M, 40 mL) before evaporation of the toluene to give 35 g of an oil. The resulting oil was

dissolved in toluene (60 mL) at room temperature and isooctane was added. The obtained slurry was cooled down to 5 °C, the crystals were filtered off and washed with isooctane. The crystals were allowed to dry under suction for 1 h. This gave 19.0 g of IIIb as white crystals (79 % yield with a HPLC purity of 98.9 %-area). Mp = 57-58°C. $^1$H-NMR ($CDCl_3$) δ 7.35 (app d, $J$ = 8 Hz, 2H), 7.22 (app d, $J$ = 8 Hz, 1H), 7.13 (app t, $J$ = 7 Hz, 1 H), 6.93-7.01 (m, 2H), 6.88 (br s, 1H), 6.55 (app d, $J$ = 8 Hz, 1 H), 4.15-4.28 (m, 4H), 3.81 (s, 2H), 2.99 (s, 3H), 1.74-1.84 (m, 4H); $^{13}$C-NMR ($CDCl_3$) δ 172.3, 142.7, 137.7, 130.8, 129.5, 128.9, 128.0, 124.2, 124.1, 122.0, 118.3, 69.1, 64.3, 38.6, 64.3, 38.6, 37.4, 25.8, 24.8.

<u>4-(Nitrooxy)butyl {2-[(2,6-dichlorophenyl)amino]phenyl}acetate (compound of formula IVb).</u>

Compound IIIb (5.0 g, 11 mmol) and lithium nitrate (2.2 g, 32 mmol) were dissolved in *N*-methylpyrrolidinone (15 mL) at 70 °C. After 23 h the reaction was cooled to 35 °C, toluene (20 mL) was added and the reaction was washed with water (2 x 30 mL). The organic layer was dried over $Na_2SO_4$ and evaporated to dryness. The resulting oil was purified by silica gel chromatography (EtOAc: Hexane; 80:20) and 4.02 g of IVb as a colorless oil was collected. $^1$H-NMR ($CDCl_3$) δ 7.34 (app d, $J$ = 8 Hz, 2H), 7.22 (app d, $J$ = 7 Hz, 1H), 7.08-7.19 (m, 1H), 6.91-7.02 (m, 2H), 6.88 (br s, 1H), 6.55 (app d, $J$ = 7 Hz, 1H), 4.38-4,46 (m, 2H), 4.14-4.21 (m, 2H), 3.81 (s, 2H), 1.71-1.82 (m, 4H); $^{13}$C-NMR ($CDCl_3$) δ 172.3, 142.7, 137.8, 130.8, 129.5, 128.9, 128.1, 124.2, 124.1, 122.1, 118.3, 72.5, 64.3, 38.6, 25.0, 23.5.

*Synthesis of 2-{2-[2-(nitrooxy)ethoxy]ethoxy}ethyl {2-[(2,6-dichlorophenyl-) amino]-phenyl}acetate (compound of formula IVc).*

<u>2-[2-(2-Hydroxyethoxy)ethoxy]ethyl {2-[(2,6-dichlorophenyl)amino]phenyl}acetate (compound of formula IIc).</u>

Thionyl chloride (1.2 mL, 16.9 mmol) was added to a suspension of Diclofenac (10 g, 33.8 mmol) and triethylene glycol (90 mL, 676 mmol) at 30°C. The reaction was stirred for 7 h before addition of aqueous potassium carbonate (0.27 M, 100 mL) and toluene (100 mL). The temperature was increased to 60°C and the water phase was discarded. The organic

phase was washed with water (3x100 mL) and concentrated to give 14.4 g of IIc as an oil. This oil was used directly in the next step. $^1$H-NMR ($CDCl_3$) δ 7.33 (app d, $J$ = 8 Hz, 2H) 7.23 (app d, $J$ = 7 Hz, 1H), 7.08-7.20 (m, 1H), 6.85-7.07 (m, 3H), 6.54 (app d, $J$ = 8 Hz, 1H), 4.31 (app t, $J$ = 5 Hz, 2H), 3.85 (s, 2H), 3.71 (m, 4 Hz, 4H), 3.54-3.64 (m, 4H), 2.50 (app br s, 1H); $^{13}$C-NMR ($CDCl_3$) δ 172.4, 142.8, 137.8, 130.9, 129.6, 128.9, 128.01, 124.2, 124.1, 122.0, 118.2, 72.5, 70.6, 70.3, 69.0, 64.3, 61.7, 38.5.

<u>10,10-Dioxido-3,6,9-trioxa-10-thiaundec-1-yl {2-[(2,6-dichlorophenyl)amino]-phenyl}acetate (compound of formula IIIc).</u>

The hydroxiester IIc (13.4 g, 31.3 mmol) from the previous step was dissolved in toluene (80 mL) together with *N*-methylmorpholine (3.5 g, 34.4 mmol) at 30°C. Methanesulfonyl chloride (3.9 g, 34.4 mmol) in toluene (10 mL) was added over 15 min. After complete addition the temperature was increased to 60°C for 2h and cooled down to 30°C overnight. Aqueous sulfuric acid (0.1 M, 40 mL) and the temperature was increased to 60°C. The water phase was discarded and the organic phase was washed with water (2x100 mL). The organic phase was concentrated to give an oil (15.3 g). This oil was purified by chromatography on silica (EtOAc/hexane; 30/70 to 50/50) to give 13.8 g of IIIc as a brown oil. $^1$H-NMR ($CDCl_3$) δ 7.34 (app d, $J$ = 8 Hz, 2H) 7.23 (app d, $J$ = 7 Hz, 1H), 7.12 (app t, $J$ = 7 Hz, 1H) 6.88-7.02 (m, 2H), 6.54 (d, $J$ = 8 Hz, 1H), 4.75-4.36 (m, 4H), 3.84 (s, 2H), 3.67-3.74 (m, 4H) 3.6 (app br s, 4 H), 3.04 (s, 3H); $^{13}$C-NMR ($CDCl_3$) δ 172.2, 142.6, 137.6, 130.8, 129.4, 128.8, 127.9, 124.1, 124.0, 121.9, 118.1, 70.4, 69.1, 68.91, 68.87, 64.2, 60.2, 38.4, 37.5.

<u>2-{2-[2-(Nitrooxy)ethoxy]ethoxy}ethyl {2-[(2,6-dichlorophenyl)amino]phenyl}acetate (compound of formula IVc).</u>

Sodium nitrate was added to a solution of the mesylate IIIc from the previous step (12.7 g, 25.1 mmol) and tetrabutylammonium nitrate in n-butylacetate (50 mL) and water (1.7 mL) at 60°C. The resulting suspension was heated to 85°C for 41 h before cooling to 60°C and addition of water (100 mL). The water phase was separated off and the organic phase was washed with water (2x100 mL). The organic phase was evaporated to dryness and the residue was crystallised from n-butylacetate (26 mL) and 2-propanol (110 mL). The crystals were filtered off, washed with 2-propanol (25 mL) and dried under reduced

pressure at 40°C to give 9,3 g of IVc as crystals. Mp = 68°C. $^{1}$H-NMR ($CDCl_3$) δ 7.34 (app d, $J$ = 8 Hz, 2H) 7.23 (app d, $J$ = 7 Hz, 1H), 7.12 (app t, $J$ = 7 Hz, 1H), 6.91-7.02 (m, 3H), 6.55 (app d, $J$ = 8 Hz, 1H), 4.58 (app t, $J$ = 5 Hz, 2H), 4.31 (app t, $J$ = 4 Hz, 2H), 3.85 (s, 2H), 3.67-3.78 (m, 4H), 3.60 (app s, 4H); $^{13}$C-NMR ($CDCl_3$) δ 172.4, 142.8, 137.8, 130.9, 129.5, 128.9, 128.0, 124.3, 124.0, 122.0, 118.3, 72.2, 70.8, 70.6, 69.1, 67.2, 64.3, 38.5

*Synthesis of 3-(nitrooxy)propyl 2-(2-benzoylphenyl)propanoate (compound of formula IVd).*

<u>3-Hydroxypropyl (2*S*)-2-(2-benzoylphenyl)propanoate (compound of formula IId)</u>

A mixture of (S)-ketoprofen (10.0 g, 39.3 mmol), 1,3-propanediol (29.9 g, 393 mmol), toluene (40 mL) and conc. sulfuric acid (0.3 g, 3.06 mmol) were heated to 80-95°C for 28h before cooling to 45°C and addition of a 5% aqueous potassium carbonate solution (50 mL). The bottom aqueous layer was separated off and the top organic layer was washed with water (2x50 mL). The organic layer was concentrated down to dryness under reduced pressure to give 11.9 g of IId as a colorless oil (96%-area LC-purity). The enantiomeric purity was >99.5 %-area. MS [$M^+$] = 312, $^{1}$H-NMR ($CDCl_3$) δ 7.78 (app t, $J$ = 7Hz, 3H), 7.41-7.68 (m, 6H), 4.30-4.79 (m, 2H), 3.81 (q, $J$ = 7 Hz, 1H), 3.51 (t, $J$ = 6 Hz, 2H), 2.35 (br s, 1H), 1.82 (quin, $J$ = 7 Hz, 2H), 1.53 (d, $J$= 7 Hz, 3H); $^{13}$C-NMR ($CDCl_3$) δ 196.7, 174.4, 140.9, 137.9, 137.4, 132.6, 131.5, 130.1, 129.1, 128.6, 128.3, 61.9, 58.9, 45.4, 31.5, 18.4, 14.2.

<u>3-[(methylsulfonyl)oxy]propyl (2*S*)-2-(2-benzoylphenyl)propanoate (compound of formula IIId).</u>

The hydroxiester IId (5.0 g, 16 mmol) from the previous step was dissolved in toluene (25 mL). Methanesulfonylchloride (2.2 g, 19.2 mmol) was added to the mixture followed by dropwise addition of N-methylmorpholine (1.78 g, 17.6 mmol). The reaction mixture was heated at 40°C for 1h and then heated to 60°C before addition of aqueous sulfuric acid (0.1 M, 20 mL) and toluene (10 mL). After extraction the mixture was separated and the organic layer was washed with aqueous potassium carbonate (0.93 g in 20 mL of water). The organic layer was concentrated under vacuum to give 5.6 g of IIId as an oil. MS [$M^+$]

= 391; $^{1}$H-NMR (300 MHz, $CDCl_3$) δ 7.78 (app t, $J = 7$ Hz, 3H), 7.41-7.69 (m, 6H), 4.21 (app t, $J = 6$ Hz, 2H), 4.18 (app t, $J = 6$ Hz, 2H), 3.82 (q, $J = 7$ Hz, 1H), 2.94 (s, 3H), 2.04 (quin, $J = 7$ Hz, 2H), 1.55 (d, $J = 7$ Hz, 3H); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 196.4, 173.8, 140.7, 138.0, 132.5, 131.4, 130.0, 129.1, 129.0, 128.6, 128.3, 66.0, 60.4, 45.3, 37.2, 28.4, 18.2.

<u>3-(nitrooxy)propyl (2*S*)-2-(2-benzoylphenyl)propanoate (compound of formula IVd).</u>
A mixture of the mesylate IIId (5.0 g, 12.8 mmol) from the previous step and lithium nitrate (2.65 g, 38.5 mmol) in *N*-methyl pyrrolidinone (15 mL) was heated at 70°C for 9h. The heating was removed and the reaction mixture was allowed to reach room temperature before addition of toluene (30 mL) and water (20 mL). The layers were separated and the organic layer was washed with water (20 mL). Concentration to dryness gave IVd as an oil (5.0 g). The enantiomeric purity was 99.5 %-area. MS [$M^+$] = 357; $^{1}$H-NMR (300 MHz, $CDCl_3$) δ 7.73-7.84 (m, 3H), 7.67 (app d, $J = 7$ Hz, 1H), 7.38-7.64 (m, 5H), 4.40 (t, $J = 6$ Hz, 2H), 4.18 (t, $J = 6$ Hz, 2H), 3.81 (q, $J = 7$ Hz, 1H), 2.94 (s, 3H), 2.01 (quin, $J = 6$ Hz, 2H), 1.55 (d, $J = 7$ Hz, 3H); $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 196.4, 173.8, 140.7, 138.0, 137.5, 132.6, 131.4, 130.0, 129.2, 129.1, 128.6, 128.3, 69.6, 60.8, 45.3, 26.3, 18.3.

CLAIMS

1. A process for the manufacturing of NO-donating compounds comprising;

$$\underset{(I)}{ML_{T1}A_{T2}\text{-}COO} + HO\text{-}X\text{-}OH \xrightarrow[\textbf{Step 1}]{} \underset{(II)}{ML_{T1}A_{T2}\text{-}COO\text{-}X\text{-}OH}$$

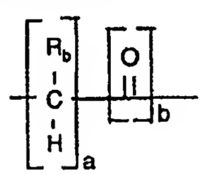
$$\underset{(II)}{ML_{T1}A_{T2}\text{-}COO\text{-}X\text{-}OH} + RSO_2Cl \xrightarrow[\textbf{Step 2}]{} \underset{(III)}{ML_{T1}A_{T2}\text{-}COO\text{-}X\text{-}O\text{-}SO_2R}$$

$$\underset{(III)}{ML_{T1}A_{T2}\text{-}COO\text{-}X\text{-}O\text{-}SO_2R} + Y\text{-}NO_m \xrightarrow[\textbf{Step 3}]{} \underset{(IV)}{ML_{T1}A_{T2}\text{-}COO\text{-}X\text{-}O\text{-}NO_m}$$

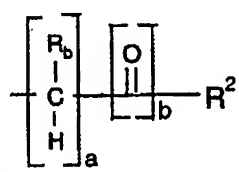
wherein:

M is a radical of a physiologically active compound;

L is O, S, (CO)O, (CO)NH, $(CO)NR^1$, NH, $NR^1$, wherein $R^1$ is a linear or branched alkyl group, or



or



wherein $R_b$ is H, $C_{1\text{-}12}$alkyl or $C_{2\text{-}12}$alkenyl;

$R^2$ is (CO)NH, $(CO)NR^1$, (CO)O, or $CR^1$ and a and b are independently 0 or 1;

A is a substituted or unsubstituted straight or branched alkyl chain;

X is a carbon linker;

R is selected from the group consisting of $C_1$-$C_8$ alkyl, phenyl, phenylmethyl, $C_1$-$C_4$ alkylphenyl, halophenyl, nitrophenyl, halogen, $CF_3$ and $n$-$C_4F_9$;

$Y\text{-}NO_3$ is lithium nitrate, sodium nitrate, potassium nitrate, magnesium nitrate, calcium nitrate, iron nitrate, zink nitrate or tetraalkylammonium nitrate (wherein alkyl is a $C_1$-$C_{18}$-alkyl, which may be straight or branched);

m is 1 or 2; and

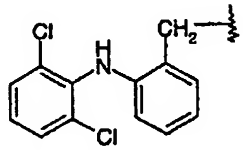
T1 and T2 are each independently 0, 1, 2 or 3;

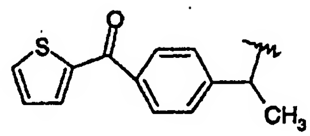
with the proviso that

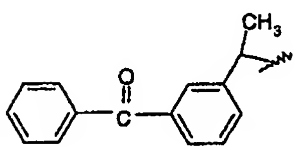
when $ML_{T1}A_{T2}$-COOH is naproxen then X is not $(CH_2)_4$.

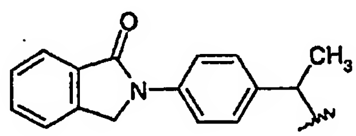
2. The process according to claim 1 wherein M is an NSAID or COX 1 or 2 inhibitor.

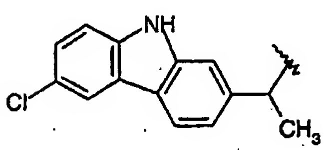
3. The process according to claim 1 wherein the group $ML_{T1}A_{T2}$ is selected from the group consisting of

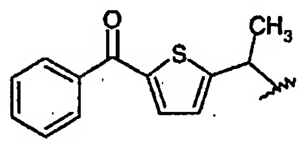


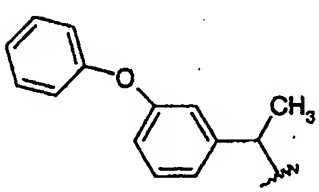


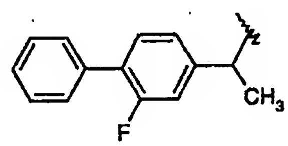


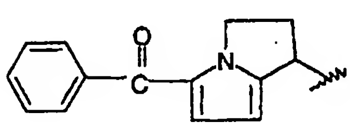


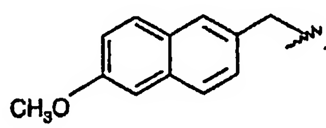


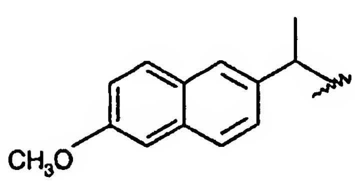


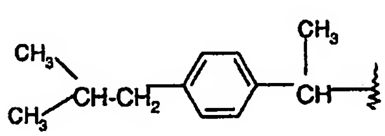


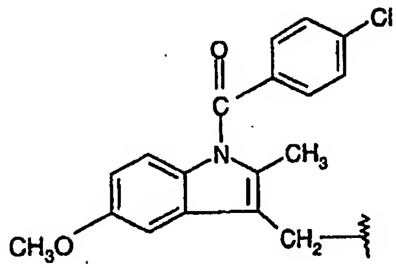




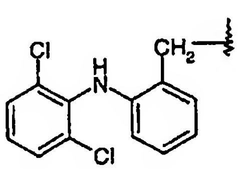


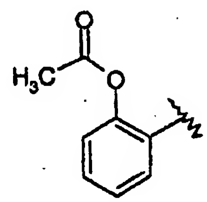


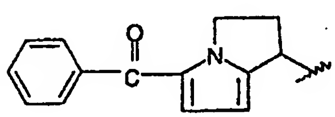


and .

4. The process according to claim 1 wherein the group $ML_{T1}A_{T2}$ is selected from the group consisting of







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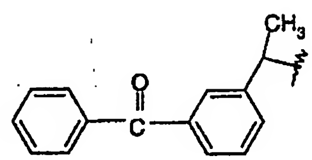
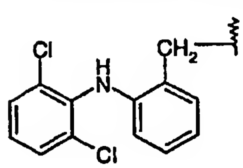
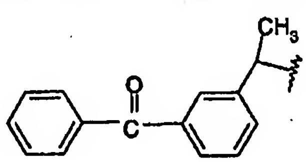
.

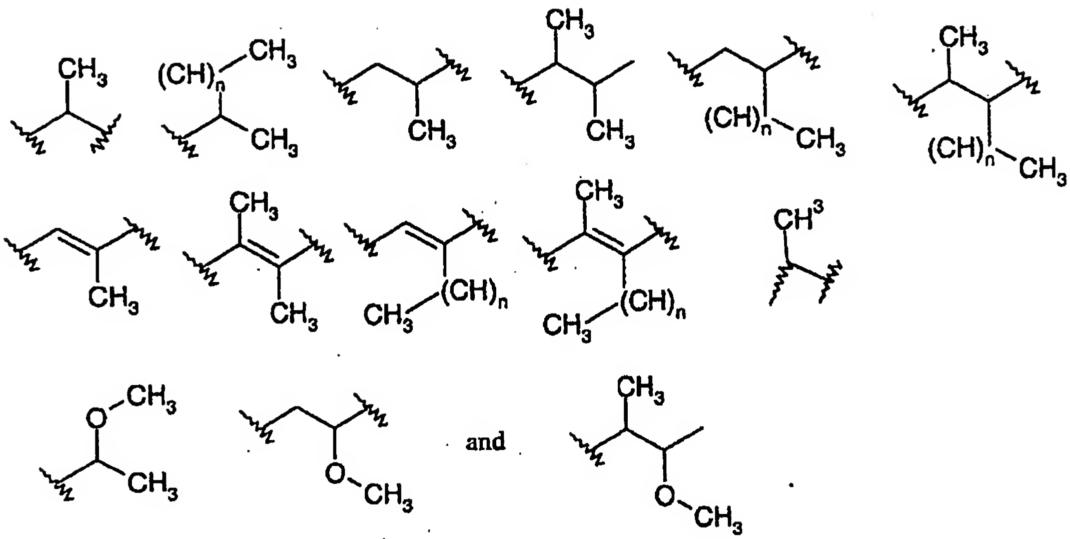
5. The process according to claim 1 wherein the group $ML_{T1}A_{T2}$ is



or

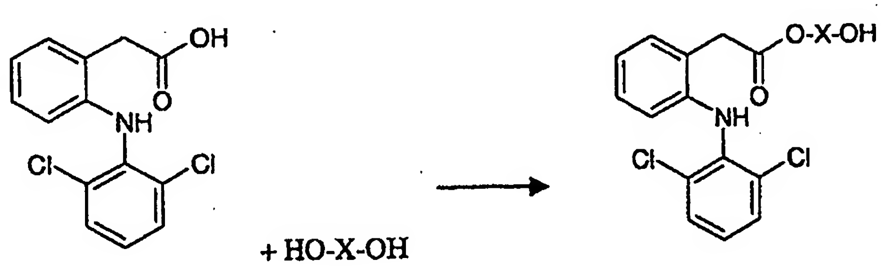
.

6. The process according to claim 1 wherein A is selected from the group consisting of $-(CH_2)_n-$, n is 0, 1, 2, 3 or 4,



7. The process according to claim 1 wherein X is selected from the group consisting of linear, branched or cyclic $-(CH_2)-_{w1}$ wherein w1 is an integer of from 2 to 10; $-(CH_2)_{w2}-O-(CH_2)_{w3}-$ wherein w2 and w3 are integers of from 2 to 10; and $-CH_2-C_6H_4-CH_2-$.

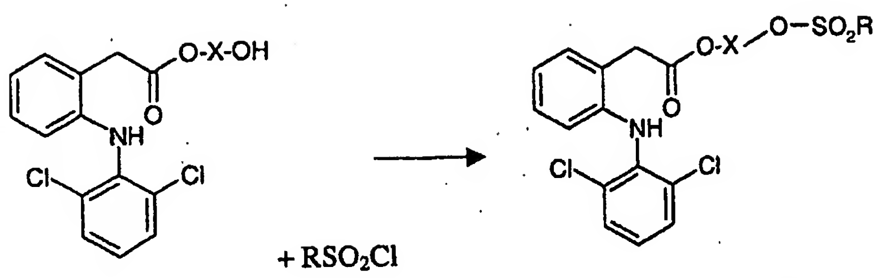
8. A process for the manufacturing of NO donating diclofenac of formula IVa, IVb and IVc, comprising:
step 1, reacting a compound of formula Ia with HO-X-OH, wherein X is $C_2H_4OC_2H_4$, $C_4H_8$ or $C_2H_4OC_2H_4OC_2H_4$, to obtain compounds of formula IIa, IIb or IIc,



diclofenac (Ia)

II,

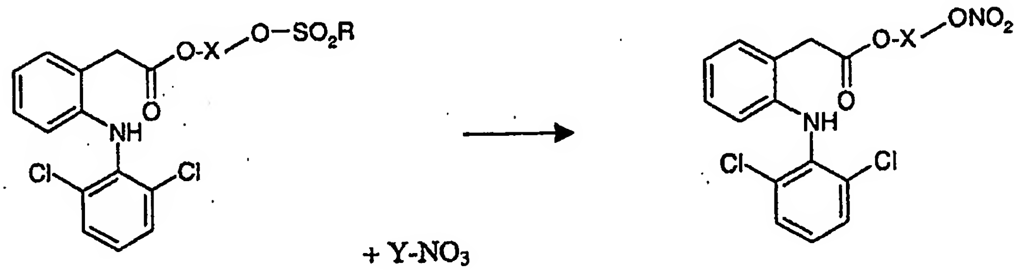
followed by,
step 2, reacting the compounds of formula IIa, IIb or IIc with $RSO_2Cl$, wherein R is as defined in claim 1, to obtain compounds of formula IIIa, IIIb or IIIc,



II III,

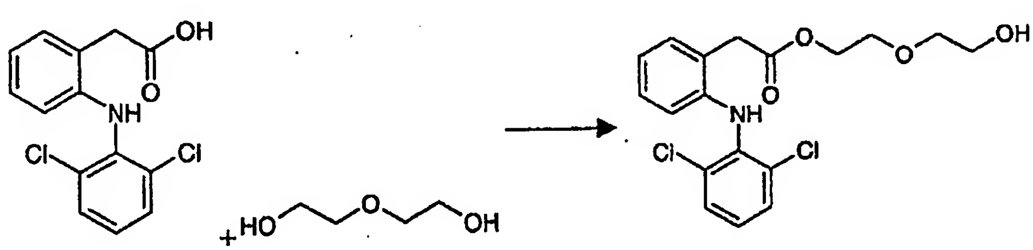
and

step 3, reacting the compounds of formula IIIa, IIIb or IIIc with a nitrate source Y-$NO_3$ as defined in claim 1, to obtain compounds of formula IVa, IVb or IVc,



III IV.

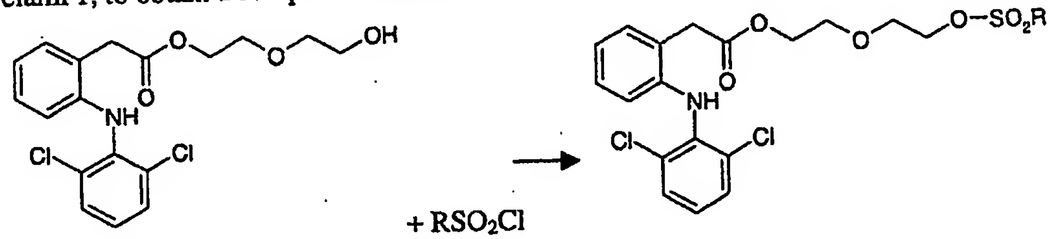
9. A process for the manufacturing of NO donating diclofenac of formula IVa comprising: step 1, reacting the compound of formula Ia with diethylene glycol to obtain a compound of formula IIa,



Ia IIa

followed by,

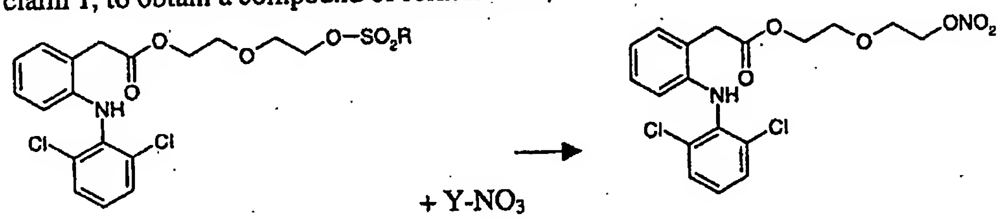
step 2, reacting the compound of formula IIa with $RSO_2Cl$, wherein R is as defined in claim 1, to obtain a compound of formula IIIa,




IIa

IIIa

step 3, reacting the compound of formula IIIa with a nitrate source $Y\text{-}NO_3$ as defined in claim 1, to obtain a compound of formula IVa,

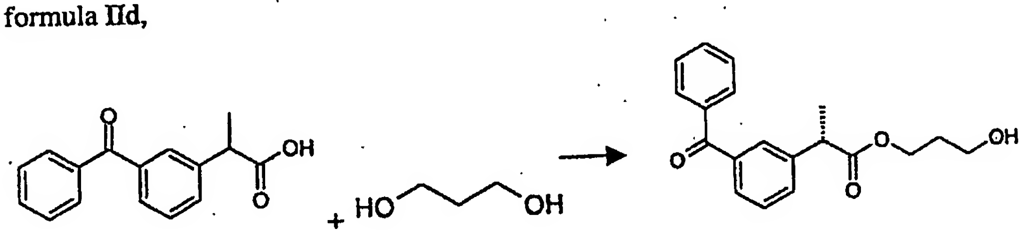



IIIa

IVa.

10. A process for the manufacturing of NO donating ketoprofen of formula IVd comprising:

step 1, reacting a compound of formula Id with 1,3-propanediol to obtain a compound of formula IId,




Id

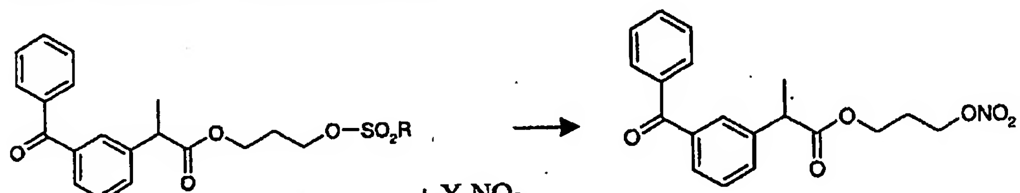
IId

followed by,

step 2, reacting the compound of formula IId with $RSO_2Cl$, wherein R is as defined in claim 1, to obtain a compound of formula IIId,

IId IIId

step 3, reacting the compound of formula IIId with a nitrate source Y-$NO_3$ as defined in claim 1, to obtain a compound of formula IVd,



+ Y-$NO_3$

IIId IVd.

11. The process according to claim 10 for the manufacturing of the *S*-enantiomer of NO donating ketoprofen of formula IVd.

12. The process according to any one of claims 1 to 11 whereby an acidic or dehydrating agent in step 1 is selected from the group comprising of sulphuric acid or its salts, perchloric acid (e.g. 70%) or other suitable acids such as polystyrene sulphonic acids, zeolites, acidic clays, sand in combination with strong hydrophilic acids such as perchloric acid or gaseous hydrogen chloride and montmorillonites.

13. The process according to any one of claims 1 to 12 whereby the solvent in step 1 is a non-polar and/or non acidic solvent.

14. The process according to any one of claims 1 to 13 whereby the solvents in step 2 are selected from a group consisting of toluene, cumene, xylenes, ethyl acetate, acetonitrile, butyl acetate and isopropyl acetate.

15. The process according to any one of claims 1 to 14 whereby the base in step 2 is triethylamine or *N*-methylmorpholine.

16. The process according to any one of claims 1 to 15 whereby a catalyst used in step 2 is 4-(dimethylamino)pyridine.

17. The process according to any one of claims 1 to 16 whereby the compound of formula III in step 2 is crystallized from an organic solvent, optionally using an antisolvent to obtain a crystalline solid having a purity of at least 95%.

18. The process according to any one of claims 1 to 17 whereby the solvent used for the crystallisation in step 2 is selected from the group consisting of toluene, cumene, xylenes, ethyl acetate, acetonitrile, butyl acetate and isopropyl acetate, or mixtures thereof.

19. The process according to any one of claims 1 to 18 whereby the antisolvent used for the crystallisation in step 2 is selected from the group comprising of ligroin, petroleum ether, halobenzenes, heptanes, hexanes, octanes, cyclohexanes, cycloheptanes and alcohols, or mixtures thereof.

20. The process according to any one of claims 1 to 19 whereby the nitrate sources in step 3 is selected from the group consisting of lithium nitrate, sodium nitrate, potassium nitrate, magnesium nitrate and calcium nitrate, or mixtures thereof.

21. The process according to any one of claims 1 to 20 whereby the organic solvent in step 3 is a polar aprotic solvent.

22. The process according to any one of claims 1 to 21 whereby the phase transfer-catalyst in step 3 is selected from the group consisting of tetraalkylammonium salt, arylalkylammonium salt, tetraalkylphosphonium salt, arylalkylphosphonium salt, crown ether, pentaethylene glycol, hexaethylene glycol and polyethylene glycol, or mixtures thereof.

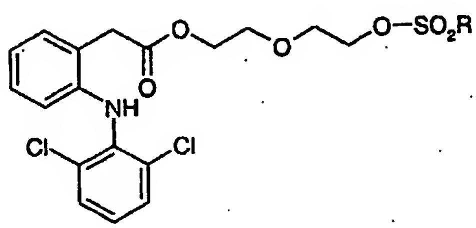
23. The process according to any one of claims 1 to 22 whereby the compound of formula IV in step 3 is extracted batch-wise or continuosly and crystallized from an organic solvent optionally using an anti solvent to obtain a crystalline solid having a purity of at least 95%.

24. The process according to any one of claims 1 to 23 whereby the solvent used for the crystallisation in step 3 is selected from the group consisting of butylacetate, isooctane, acetone and water, or mixtures thereof.

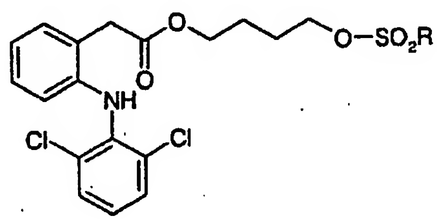
25. The process according to any one of claims 1 to 24 whereby the anti solvent used for the crystallisation in step 3 is selected from the group consisting of 2-propanol, isooctane, heptane and water, or mixtures thereof.

26. The process according to any one of claims 1 to 25 whereby the temperature is between -40°C and 120°C.

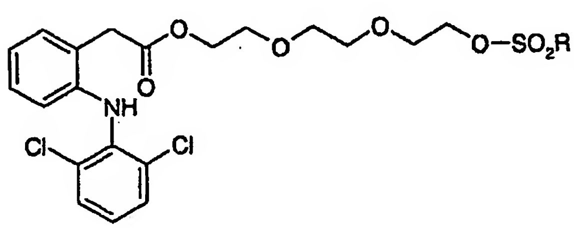
27. Compounds of formula IIIa, IIIb, IIIc and IIId:



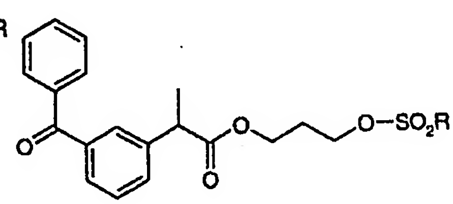
IIIa



IIIb



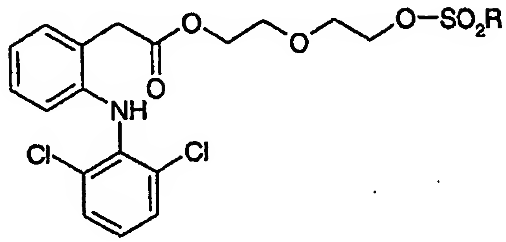
IIIc



IIId

wherein R is selected from the group consisting of $C_1$-$C_8$ alkyl, phenyl, phenylmethyl, $C_1$-$C_4$ alkylphenyl, halophenyl, nitrophenyl, halogen, $CF_3$ and $n$-$C_4F_9$.

28. Compound of formula IIIa,



IIIa

wherein R is selected from the group consisting of $C_1$-$C_8$ alkyl, phenyl, phenylmethyl, $C_1$-$C_4$ alkylphenyl, halophenyl, nitrophenyl, halogen, $CF_3$ and $n$-$C_4F_9$.

29. Use of the compounds of formula III, $ML_{T1}A_{T2}$-X-O-$SO_2$R, wherein M, L, A, T1, T2, X and R are as defined in claim 1, as an intermediate for the manufacturing of a pharmaceutically active compound.

30. Use of the compounds of formula IIIa, IIIb, IIIc and IIId, according to claims 27 or 28, as an intermediate for the manufacturing of 2-[2-(nitrooxy)ethoxy]ethyl {2-[(2,6-dichlorophenyl)amino]phenyl}acetate, 4-(nitrooxy)butyl {2-[(2,6-dichlorophenyl)amino]-phenyl}acetate, 2-{2-[2-(nitrooxy)ethoxy]ethoxy}ethyl {2-[(2,6-dichlorophenyl)amino]-phenyl}acetate, 3-(nitrooxy)propyl 2-(2-benzoylphenyl)propanoate and 3-(nitrooxy)propyl (2*S*)-2-(2-benzoylphenyl)propanoate.

31. Use of intermediate compounds of formula IIIa, IIIb, IIIc and IIId as defined in claims 27 or 28, prepared according to the process according to any one of claims 1 to 26, for the manufacturing of a medicament for the treatment of pain and inflammation.

32. Use of the process according to any one of claims 1 to 26, for the large scale manufacturing of NO donating compounds of formula IV.

33. Use of the process according to any one of claims 1 to 26, for the large scale manufacturing of NO donating compounds of formula IVa, IVb, IVc and IVd.

ABSTRACT

The present invention relates to a new process for the preparation of NO donating compounds and to new intermediates obtained and used therein. The invention further relates to the use of the new intermediates for the manufacturing of pharmaceutically active compounds.

The invention also relates to the use of NO donating compounds prepared according to the process of the present invention for the manufacturing of a medicament for the treatment of pain and inflammation.